

[C A S E R E P O R T]

Fluconazole-induced Fixed Drug Eruption

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ABSTRACT

Triazole antifungals are commonly used in the treatment of oral, esophageal, and vaginal candidiasis. Fluconazole is frequently prescribed as the therapy modality for vaginal fungal infections. On rare occasions, fluconazole has been shown to cause fixed drug eruptions. Lesions of fixed drug eruptions vary in size and number, but have the same general appearance and symptoms. The authors report a case of fluconazole-induced fixed drug eruption in a 24-year-old woman with recurrent vaginal candidiasis. The lesion was initially diagnosed as a spider bite. Topical and oral provocation tests with fluconazole were performed. Topical provocation with petroleum/fluconazole and dimethyl sulfoxide/fluconazole were both negative. Oral provocation was positive, thus confirming the diagnosis of fluconazole-induced fixed drug eruption. (*J Clin Aesthet Dermatol.* 2013;6(3):44–45.)

A 24-year-old Caucasian woman presented with a recurrent, pruritic, cutaneous lesion on the right palmar surface. A single, 2cm, nummular, erythematous lesion was present over the thenar eminence (Figure 1). This was the fifth time this lesion had occurred. Each recurrence was in the same spot, lasting about 10 days. The outbreaks presented in a sporadic fashion, with no noticeable pattern. Lesion diameter and symptom severity increased with each recurrence. After the third eruption, the patient was seen by a physician. She was diagnosed with a spider bite, possibly black widow, with retained fang, as the reason for the recurrence. After a detailed history was obtained, it was noted that each skin eruption followed treatment (150mg oral fluconazole) for vaginal candidiasis.

The patient's current eruption was similar to her previous outbreaks with pruritis, slowly increasing in intensity, (24 hours post-ingestion) and erythema (48 hours post-ingestion). Fine and crude touch of the lesion resulted in intense itching and pain. The patient observed that the pruritis increased in intensity during ultraviolet stimulation from a tanning bed. Around 60 hours post-ingestion the patient documented a new sign that was not present in previous eruptions; the lesion developed a 2mm edematous, yellowish, fluid-filled ring around the erythematous portion, resembling a bullseye (Figure 2). The remainder of the course followed its typical pattern; symptoms residing by Day six, resolution of erythema by Day 10 with sloughing of the skin at the lesion site by Day 12 (Figure 3). After each episode, a faint postinflammatory

pigmented patch remained.

Topical provocation was done with 10% fluconazole in petroleum and dimethyl sulfoxide (DMSO) at the dormant lesion site, using the open test method.¹ Fluconazole was mixed with white petroleum after heating the petroleum to a liquid consistency. After cooling, the mixture was placed directly on the lesion site. The fluconazole/petroleum mixture did not elicit a response. Fluconazole was then mixed with DMSO and the solution was applied to the lesion site using a cotton swab applicator. This also did not provoke an eruption.

Oral provocation test, with 50mg fluconazole (one-third therapeutic dose), was positive. The patient experienced severe pruritis 45 minutes post-ingestion with erythema occurring several hours later. A large blister formed on Day 3, covering half of the lesion. As per the patient, this was the first time a blister this large had formed.

Cross reactivity has been documented with structurally related triazoles, such as itraconazole.² The authors tested for cross reactivity with topical and oral itraconazole provocation. Topical testing was done using 10% itraconazole in petroleum and DMSO. The itraconazole/petroleum mixture did not elicit a response nor did the itraconazole/DMSO solution. Oral provocation with 100mg (one half therapeutic dose) capsule also did not induce a fixed drug eruption in this patient.

DISCUSSION

Triazole antifungals are commonly used in the treatment of oral, esophageal, and vaginal candidiasis.

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They are composed of a five-membered ring, consisting of two carbon atoms and three nitrogen atoms, with varying side chains. Fluconazole and voriconazole are readily absorbed and exhibit high bioavailability, whereas itraconazole and posaconazole have generally lower oral bioavailability.³ This bioavailability may have an impact on the toxicity of these drugs.

Fixed drug eruption is considered a form of delayed-type hypersensitivity, mediated by CD8+ T cells. It is characterized by single or multiple, sharply demarcated, pruritic, erythematous, nummular plaques. Fixed drug eruption occurs when patients become sensitized to a particular drug or its metabolites. Intermittent drug administration is more likely to cause sensitization than continuous administration. The lesions recur in the same spot, usually within 30 minutes to 12 hours post-drug exposure. Pruritis and burning usually precede the appearance of the lesions. Clinical resolution yields postinflammatory pigmentation. The lesions remain quiescent until re-exposure of the causative agent. The most favored sites are the hands, feet, genitalia, and perineal area.⁵

Dermal biopsy of a lesion will demonstrate spongiosis, hydropic degradation of the basal layer and a lymphocytic perivascular infiltrate with dermal macrophages.⁶ Intraepidermal CD8+ T cells with effector-memory phenotyping reside along the epidermal side of the dermoepidermal junction. They are a major contributor in the development of localized tissue damage with the direct killing of nearby keratinocytes and release of large amounts of cytokines. During the initial phase of fixed drug eruption, mast cells are thought to contribute to the activation of intraepidermal CD8+ T cells. Once sensitization occurs, the size and the number of skin lesions tends to become greater with recurrence than with the first attack.⁷

CONCLUSION

Fixed drug eruption induced from fluconazole is not a common occurrence. When it does occur, it can be easily overlooked and diagnosed incorrectly. The lesions can occur on any body surface and cause the patient significant physical and mental discomfort. Physicians should be aware of this possibility so that occurrences may be readily diagnosed and future recurrences avoided.

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Figure 1. Day 2 postingestion of 150mg oral Fluconazole. Recurrence of a 2cm erythematous lesion over the right thenar eminence



Figure 2. Day 3 postingestion. Edematous fluid-filled ring surrounding erythematous rash, resembling a bullseye



Figure 3. Day 21 postingestion. Sloughing of the skin at the lesion site